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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/606,630	06/26/2003	Spiros Liras	PC10085C	4988

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EXAMINER	
MCKENZIE, THOMAS C	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 10/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/606,630	LIRAS ET AL.	
	Examiner	Art Unit	
	Thomas McKenzie, Ph.D.	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,16,17,19-21 and 23-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-13 and 22* is/are allowed.

6)☒ Claim(s) *14,16,17,19-21 and 23-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/26/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to amendments filed on 8/9/04. Applicant has amended claims 1, 14, 16, and 19-21. Applicant has canceled claims 15 and 18. Claims 22-25 are new. Claims 1-14 16, 17, and 19-21 were previously rejected. There are twenty-three claims pending and twenty-three under consideration. Claims 1-13 and 22 are compound claims. Claims 14, 19, and 23 are composition claims. Claims 16, 17, 20, 21, 24, and 25 are method of using claims. This is the second action on the merits. The application concerns some bis-phenyl piperidine and morpholine compounds, compositions, and uses thereof.

Response to Amendment

2. Applicants' amendment of the first line of the specification overcomes the objection made in point #3 of the previous office action. Applicants' cancellation of the relevant claims renders moot the objection made in point #4. Applicants' amendments overcomes the indefiniteness rejections made in points #6-#9 of the previous office action. Applicants' deletion of prevention from claims 19 and 21 overcomes the enablement rejection made in point #12. Applicants' terminal disclaimer overcomes the double patenting rejections made in points #13 and #14. Applicants present requirement that both aromatic rings in formula I have mandatory substituents overcomes the art rejection over Kametani (Yakugaku

Zasshi) made in point #15. The prior art does not teach or suggest substituents upon both rings.

Claim Objections

3. Objection remains to claim 19 and objection is newly raised to claim 23 under 37 CFR 1.75 as being a substantial duplicate of claim 14. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). The phrase "for treating a disorder ... etc." is a statement of intent. This is a purely mental act with no physical consequences. Thus, claims 19 and 23 are composition claims with the same limitations as claim 14.

Applicants argue that the two claims require differing amount of active ingredients and therefore are not identical. This is not persuasive because the features upon which applicant relies (i.e., the concentration of the active substances) are not recited in the objected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). In addition, nowhere does the specification indicate what, if any, differences in concentration are required for these differing alleged uses.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17 and 21 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specification does not set forth any steps involved in determining how to identify "a disorder or condition, the treatment or prevention of which can be effected or facilitated by modulating binding to opioid receptors in a mammal". It is unclear what diseases and treatments applicant is intending to encompass. For example, in lines 15-19, page 7 Applicants discuss such diseases but do not list what they are specifically or describe how they can be identified.

Determining whether a given disease responds or does not respond to such a receptor antagonist and thus, is covered by the claim language, can only be accomplished through potentially inconclusive clinical research. Suppose that a given drug, which has receptor antagonist properties *in vitro*, when administered to a patient with a certain disease, does not produce a favorable response. One cannot conclude that specific disease does not fall within this claim. Keep in mind that:

A. It may be that the next patient will respond. No pharmaceutical has 100% efficacy. What success rate is required to conclude our drug is a treatment?

Thus, how many patients need to be treated? If "successful treatment" is what is intended, what criterion is to be used? If one person in 10 responds to a given drug, does that mean that the disease is treatable? One in 100? 1,000? 10,000? Will the standard vary depending on the current therapy for the disease?

B. It may be that the wrong dosage or dosage regimen was employed. Drugs with similar chemical structures can have markedly different pharmacokinetics and metabolic fates. It is quite common for pharmaceuticals to work and or be safe at one dosage, but not at another that is significantly higher or lower. Furthermore, the dosage regimen may be vital --- should the drug be given e.g. once a day, or four times in divided dosages? The optimum route of administration cannot be predicted in advance. Should our drug be given as a bolus *iv* or in a time-release *po* formulation. Thus, how many dosages and dosage regimens must be tried before one is certain that our drug is not a treatment for this specific disease?

C. It may be that our specific drug, while active *in vitro*, simply is not potent enough or produces such low concentrations in the blood that it is not an effective treatment of the specific disease. Perhaps a structurally related drug is potent enough or produces high enough blood concentrations to treat the disease in question, so that the first drug really does fall within the claim. Thus, how many

different structurally related receptor antagonists must be tried before one concludes that a specific disease does not fall within the claim?

D. Conversely, if the disease responds to our second drug but not to the first, both of whom are receptor antagonists *in vitro*, can one really conclude that the disease falls within the claim? It may be that the first compound result is giving the accurate answer, and that the success of second compound arises from some other unknown property that the second drug is capable. It is common for a drug, particularly in the CNS, to work by many mechanisms. The history of psychopharmacology is filled with drugs, which were claimed to be a pure receptor XYX agonist or antagonist, but upon further experimentation shown to effect a variety of biological targets. In fact, the development of a drug for a specific disease and the determination of its biological site of action usually precede linking that site of action with the disease. Thus, when mixed results are obtained, how many more drugs need be tested?

E. Suppose that our drug is an effective treatment of the disease of interest, but only when combined with some very different drug. There are for example, agents in antiviral and anticancer chemotherapy that are not themselves effective, but are effective treatments when the agents are combined with something else.

F. Even the most desired outcome does not unequivocally establish the meaning of the phrase. Our drug alone could be an effective treatment of the disease of interest. One still cannot conclude that the disease cured is a "Factor X mediated disease". What if our drug has a second biological effect in addition to d-opioid receptor inhibition? It is possible that this second mechanism is responsible for the positive outcome.

Determining whether a given disease responds or does not respond to such a receptor antagonist and thus, covered by the claim language, will require extensive and potentially inconclusive clinical research. With out such clinical research to identify the patients and diseases Applicants intend to treat, the physician skilled in the clinical arts cannot determine the metes and bounds of the claim. Hence, the claims are indefinite.

Applicants argue that "the Background of the Invention section, sets forth a multiplicity of references which guide those skilled in the art to the relationship between the diseases indicated and the modulation of opioid receptor binding." This is not percussive for three reasons. Firstly, the only recitation linking specific diseases and δ-opioid receptors in found in lines 18-21, page 1, "[a]ctivation of delta receptors produces antinociception in rodents and can induce analgesia in man, in addition to influencing motility of the gastrointestinal tract. (See Burks, T.

F. (1995) in "The Pharmacology of Opioid Peptides", edited by Tseng, L. F., Harwood Academic Publishers)." By multitude, do Applicants mean one only? Secondly, are claims 17 and 21 limited to analgesia alone? Nociception means "a peripheral nerve organ or mechanism for the reception and transmission of painful or injurious stimuli" according to the On-Line Medical Dictionary. Thus, antinociception must also mean analgesia. "[M]otility of the gastrointestinal tract" is a normal physiological action, not a disease. Thus, the only disease Tseng teaches as related is analgesia. Thirdly, the incorporation of essential material in the specification by reference to a publication is improper. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14, 16, 17, and 19-21 remain rejected and claims 23-25 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating pain, does not reasonably provide enablement for treating all other listed diseases. The specification does not enable any physician skilled in the art of medicine, to make the invention commensurate in scope with these claims.

The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. The four main issues are the lack of correlation between clinical efficacy for disease treatment and Applicants' δ-opioid receptor assay, the lack of any biological data, the state of the prior art concerning δ-opioid receptor antagonists, and very broad scope of the diseases to be treated.

a) Determining if any particular claimed compound would treat any particular claimed disease would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it clinical trials with a number of fundamentally different diseases, or to testing them in an assay known to be correlated to clinical efficacy of such treatment. This is a large quantity of experimentation. b) The direction concerning treating diseases is found in the passage spanning line 32, page 2 to line 10, page 3, lines 7-22, page 6, and lines

22-34, page 8, which merely states Applicants' intention to do so. Applicants describe formulations in the passage spanning line 6, page 33 to line 10, page 34. Doses required to practice their invention are described in lines 11-15, page 34. A 50,000-fold range of doses is recommended. Since no δ-opioid receptor ligand has ever been used to treat any human disease, how is the skilled physician to know what dose to use for each of these different diseases? There is an *in vitro* receptor binding assay described in line 19, page 30 to line 13, page 31 with no data. There are two *in vitro* organ bath assays described in lines 16-38, page 31 with no data. There is an *in vitro* cell function assay described in line 5, page 32 to line 6, page 33, again with no data. Applicants do not assert and it is not recognized in the pharmaceutical arts that these assays are correlated to clinical efficacy for treatment of all claimed diseases. c) There is no working example of treatment of any disease in man or animals. d) The nature of the invention is clinical treatment of disease with inhibitors of the δ-opioid receptor, which involves physiological activity. e) The state of the clinical arts in δ-opioid receptor diseases is provided by Kowaluk (Ann. Reports Med. Chem.) who reports in the second complete paragraph on page 12, that analgesia is the only recognized used of such agonists. Applicants in lines 25-30, page 1 admit that pain relief is the only art recognized use of δ-opioid receptor agonists.

f) The artisan using Applicants invention would be a physician with a MD degree and several years of experience. g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). h) The scope of the claims involves all of the hundreds of thousands of compounds of claim 1 as well as the thousands of diseases embraced by the term inflammatory disease, respiratory and gastrointestinal disorders etc. Thus, the scope of claims is enormous.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Applicants make two arguments concerning this rejection. Firstly, they point to Burks, T. F. (1995) in "The Pharmacology of Opioid Peptides", edited by Tseng, L. F., Harwood Academic Publishers) cited in lines 18-21, page 1 of the

specification as providing enablement for their huge number of claimed disease therapies. Secondly they cite *Atlas Powder Company v. E.I. Du Pont De Nemours & Company* 224 USPQ 409, in support of their contention that a few inoperative embodiments do not constitute grounds for an enablement rejection. To the first argument, Burks, T. F. (1995) in "The Pharmacology of Opioid Peptides", edited by Tseng, L. F., Harwood Academic Publishers) teaches "[a]ctivation of delta receptors produces antinociception in rodents and can induce analgesia in man, in addition to influencing motility of the gastrointestinal tract. Nociception means "a peripheral nerve organ or mechanism for the reception and transmission of painful or injurious stimuli", according to the On-Line Medical Dictionary. Thus, antinociception must also mean analgesia. "[M]otility of the gastrointestinal tract" is a normal physiological action, not a disease. Thus, the only disease Tseng teaches as enabled is analgesia.

Concerning the second argument, Applicants have turned the holdings of the U.S. Court of Appeals for the Federal Circuit in *Atlas Powder Company v. E.I. Du Pont De Nemours & Company* 224 USPQ 409 on its head. Applicants claimed inflammatory diseases embrace thousands of diseases. Applicants claimed respiratory and gastrointestinal diseases embrace hundreds of different and unrelated diseases. Applicants have provided evidence for enablement for

treatment of a single medical condition, namely pain. In *Atlas Powder Company v. E.I. Du Pont De Nemours & Company* 224 USPQ 409 the U.S. Court of Appeals for the Federal Circuit held, "[e]ven if some of the claimed combinations were inoperative, the claims are not necessarily invalid" In *Atlas Powder Company v. E.I. Du Pont De Nemours & Company* 224 USPQ 409, the earlier district court trial had identified Bancroft's Rule which was a "basic principle of emulsion chemistry," allowing the skilled artisan to identify the inoperative embodiments. In the present application almost every one of the thousands of claimed embodiments is inoperative. In the present case Applicants have cited no scientific rule, which would identify which inflammatory, respiratory, and gastrointestinal disease would respond to Applicants antagonists and which would not.

Allowable Subject Matter

6. Claims 1-13 and 22 are allowed.

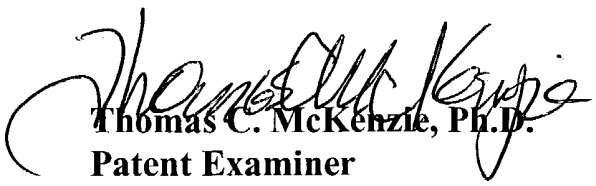
Conclusion

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

9. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (703) 872-9306. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 8:30 to 5:30, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact Mukund Shah SPE of 1624 at (571)-272-0674.



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